UREMIC TOXINS: HOW TO CLEAR THEM DURING HEMODIALYSIS

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Uremic toxins, introduction
Introduction

Homeostasis of fluid, electrolytes & acid-base

Endocrine function

Waste product removal

Water-soluble

Middle molecule

Protein-bound

“Uremic toxins”
Introduction

Water-soluble

MW < 500 Da
Diffusion
Concentration gradient
Urea

Middle molecule

MW > 500 Da
Convection
Pressure gradient
B2-microglobulin

Protein-bound

< 500 Da, protein-bound
Difficult to remove
Indoxyl sulfate, p-cresylsulfate
Pathophysiology

CARDIOVASCULAR DISEASE
OXIDATIVE STRESS
METABOLIC DISEASE
INFLAMMATION
INFECTION
FIBROSIS
Which uremic toxins are making our patient sick?

- Confounding factors (pre-existing CV disease)
- Large inter-patient variability
- Inability to decrease a single compound
- Complex and multifactorial interplay between different key elements, present for longer time
Which uremic toxins are making our patients sick?

- No confounding factors or co-morbidities
- Isolated kidney disease
- Growth

Opportunities in pediatric population
Enhancing uremic solute removal improves growth

doi: 10.1093/ndt/gfp565
Advance Access publication 4 November 2009

**Daily online haemodiafiltration promotes catch-up growth in children on chronic dialysis**

Michel Fischbach, Joelle Terzic, Soraya Menouer, Céline Dheu, Laure Seuge and Ariane Zalosczie

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*Figure 2* Daily intensive online hemodiafiltration (IOD) promotes catch-up growth (from reference 12).
In pediatrics?

Pediatric Nephrology (2018) 33:921–924
https://doi.org/10.1007/s00467-018-3920-8

EDITORIAL COMMENTARY

A plea for more uremic toxin research in children with chronic kidney disease

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UToPaed study: uremic toxins in pediatric CKD

more advanced and appropriate tools to improve management of children with CKD
Uremic toxins, how to clear them?
How to clear uremic toxins?

1. Solute removal in the dialyzer
2. Solute transport in the patient

Kinetics
Total solute removal (mass)

Clearance & extraction ratio
Solute transport in the dialyzer

Clearance and extraction ratio $\approx$ blood flow + membrane + dialysate flow

Dialyzer fiber length, diameter and permeability

Adding convection to diffusion

Eloot et al., Comp Meth Biomech Biomed Eng 2006; Leypoldt et al., Kidney Int, 1999
Solute transport in the dialyzer

Diffusion = well established removal strategy of free fraction protein-bound uremic toxins

Table 2. Instantaneous clearance (mL/min) at 60 min

<table>
<thead>
<tr>
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<th>Post-HDF</th>
<th>Pre-HDF</th>
<th>Pre-HF</th>
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<tbody>
<tr>
<td>Urea</td>
<td>243.0 ± 18.7</td>
<td>230.1 ± 10.5*</td>
<td>150.7 ± 15.0**&lt;sup&gt;§§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Creatinine</td>
<td>179.4 ± 48.3</td>
<td>148.9 ± 22.3*</td>
<td>103.7 ± 19.9**&lt;sup&gt;§§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Uric acid</td>
<td>166.4 ± 14.1</td>
<td>153.4 ± 9.8*</td>
<td>104.8 ± 8.9**&lt;sup&gt;§§&lt;/sup&gt;</td>
</tr>
<tr>
<td>β₂M</td>
<td>82.8 ± 16.1</td>
<td>67.2 ± 18.5*</td>
<td>87.5 ± 9.6&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hippuric acid</td>
<td>131.2 ± 15.6</td>
<td>121.4 ± 13.1*</td>
<td>68.7 ± 23.9&lt;sup&gt;§§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Indole acetic acid</td>
<td>66.6 ± 8.6</td>
<td>67.5 ± 9.3</td>
<td>38.8 ± 5.4**&lt;sup&gt;§§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Indoxylsulfate</td>
<td>33.4 ± 7.4</td>
<td>34.7 ± 9.9</td>
<td>18.7 ± 6.6**&lt;sup&gt;§§&lt;/sup&gt;</td>
</tr>
<tr>
<td>p-Cresylsulfate</td>
<td>23.5 ± 4.6</td>
<td>24.6 ± 6.4</td>
<td>12.9 ± 2.5**&lt;sup&gt;§§&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Pre-HDF versus post-HDF: *P < 0.017, **P < 0.001; pre-HF versus post-HDF: †P < 0.017, ‡P < 0.001; pre-HF versus pre-HDF: §P < 0.017, §§P < 0.001.

Meyer et al., Seminars in dialysis 2011; Sirich et al., NDT, 2012; Meert et al., NDT, 2009
Solute transport in the dialyzer

Research question: does post-HDF decrease levels of protein-bound uremic toxins?

Snauwaert et al., NDT, 2020 Apr 1;35(4):648-656.
Solute transport at the dialyzer

Snauwaert et al., NDT, 2020 Apr 1;35(4):648-656.
Solute transport in the patient

Generation (G)

PLASMATIC COMPARTMENT

Inter-compartmental clearance ($K_{12}$)

BLOOD CELLS, ALBUMIN

Dialyzer ($K_{dialyzer}$)

Renal ($K_{renal}$)

OTHER DEEPER TISSUES

Eloot et al., Seminars in Dialysis, 2012
Solute transport in the patient

Two-compartment kinetic model

Removal will be limited for solutes with
- Large distribution volume
- Slow intercompartmental clearance ($K_{12}$)

Eloot et al., Seminars in Dialysis, 2012; Eloot et al., PLOS one, 2016
Solute transport in the patient

Slow intercompartimental clearance (K12) = slow transport into the plasma

Eloot et al., PLOS one, 2016
Solute transport in the patient

Patient needs time to mobilize uremic toxins into the plasma

Eloot et al., Kidney International, 2008
Solute transport in the patient

Dialyzer clearance shows an inverse relation with % protein-binding

Eloot et al., PLOS one, 2016
A Sad but Forgotten Truth: The Story of Slow-Moving Solutes in Fast Hemodialysis

Sunny Eloot, Wim Van Biesen, and Raymond Vanholder
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Does the Adequacy Parameter $Kt/V_{\text{urea}}$ Reflect Uremic Toxin Concentrations in Hemodialysis Patients?

Sunny Eloot*, Wim Van Biesen, Griet Glorieux, Nathalie Neirynck, Annemieke Dhondt, Raymond Vanholder

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Abstract

Hemodialysis aims at removing uremic toxins thus decreasing their concentrations. The present study investigated whether $Kt/V_{\text{urea}}$, used as marker of dialysis adequacy, is correlated with these concentrations. Predialysis blood samples were taken before a midweek session in 71 chronic HD patients. Samples were analyzed by colorimetry, HPLC, or ELISA for a broad range of uremic solutes. Solute concentrations were divided into four groups according to quartiles of $Kt/V_{\text{urea}}$, and also of different other parameters with potential impact, such as age, body weight (BW), Protein equivalent of Nitrogen Appearance (PNA), Residual Renal Function (RRF), and dialysis vintage. Dichotomic concentration comparisons were performed for gender and Diabetes Mellitus (DM). Analysis of Variance in quartiles of $Kt/V_{\text{urea}}$ did not show significant differences for any of the solute concentrations. For PNA, however, concentrations showed significant differences for urea ($P < 0.001$), uric acid (UA), p-cresylsulfate (PCS), and free PCS (all $P < 0.01$), and for creatinine (Crea) and hippuric acid (HA) (both $P < 0.05$). For RRF, concentrations varied for β₂-microglobulin ($P < 0.001$), HA, free HA, free indoxyl sulfate, and free indole acetic acid (all $P < 0.01$), and for p-cresyl glucuronide (PCG), 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF), free PCS, and free PCG (all $P < 0.05$). Gender and body weight only showed differences for Crea and UA, while age, vintage, and diabetes mellitus only showed differences for one solute concentration (UA, UA, and free PCS, respectively). Multifactor analyses indicated a predominant association of concentration with protein intake and residual renal function. In conclusion, predialysis concentrations of uremic toxins seem to be dependent on protein equivalent of nitrogen appearance and residual renal function, and not on dialysis adequacy as assessed by $Kt/V_{\text{urea}}$. Efforts to control intestinal load of uremic toxin precursors by dietary or other interventions, and preserving RRF seem important approaches to decrease uremic solute concentration and by extension their toxicity.
Current markers are poor predictors of overall uremic toxin accumulation

Snauwaert et al. 2018 (Ped Nephrol)
Alternative strategies to decrease uremic toxicity?

Figure 2 | Removal parameters. (a) Total solute removal (mg, except for urea in 0.1 g), (b) total cleared volume (ml), (c) dialyzer extraction ratio, (d) and reduction ratio (%) of urea, creatinine, phosphorus, and β2-microglobulin for the 4, 6, and 8 h dialysis session.

Eloot et al., Kidney Int, 2016; Fischbach et al., 2009
Alternative strategies to decrease uremic toxicity?

**MEMBRANES WITH ADSORPTIVE CAPACITY**

- Particle-free polymeric membrane layer
- MMM layer
- Embedded activated carbon particle

**PRESERVATION OF RESIDUAL KIDNEY FUNCTION**

**DIETARY FIBER, PRE-, PRO, and SYNBIOTICS**

Jansens et al. 2016; Tijink et al. 2014
Conclusion and take-home message

With even the most recent advances, it seems that small solute removal in the dialyzer is close to its optimum.

eGFR and Kt/V are poor predictor of overall uremic toxin accumulation and removal.

Solute transport in the patient limits the increase of performance with the traditional dialytic approaches.
TEAMWORK DIVIDES THE TASK & DOUBLE THE SUCCESS

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All patients and families participating & their local team
THANK YOU!

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